THE GASTROENTEROLOGY ANNUAL/3

A series of critical surveys
of the international literature

Edited by

F. KERN Jr

A.L. BLUM

THE GASTROENTEROLOGY ANNUAL/3

A series of critical surveys
of the international literature

Edited by

F. KERN Jr
Department of Medicine, University of Colorado
School of Medicine, Denver, Colorado, U.S.A.

A.L. BLUM
Department of Medicine, Triemli Hospital
Zurich, Switzerland

ELSEVIER
Amsterdam - New York - Oxford

ISBN 0 444 90397 6

Notice

The editors and the publisher of this work have made every effort to ensure that the drug dosage schedules herein are accurate and in accord with the standards accepted at the time of publication. Readers are advised, however, to check the product information sheet included in the package of each drug prior to administration to be certain that changes have not been made in either the recommended dose or contraindications. Such verification is especially important in regard to new or infrequently used drugs.

Published by:
Elsevier Science Publishers B.V.
P.O. Box 1126
1000 BC Amsterdam

Sole distributors for the USA and Canada:
Elsevier Science Publishing Co. Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in The Netherlands by Casparie Amsterdam

Contributors

T.P. ALMY
Veterans Administration Medical Center
White River Junction, VT 05001
U.S.A.

J.A. BARROWMAN
Faculty of Medicine
Memorial University of Newfoundland
St Johns
Newfoundland
Canada

M.J. BLASER
Infectious Disease Section (III L)
Veterans Administration Medical Center
1055 Clermont Street
Denver, CO 80220
and
Department of Medicine
University of Colorado School of Medicine
Denver, CO 80220
U.S.A.

C.R. BOLAND
Gastrointestinal Unit
Veterans Administration Medical Center
2215 Fuller Road
Ann Arbor, MI 28105
U.S.A.

R.S. BRESALIER
University of California Service
Veterans Administration Medical Center
4150 Clement Street (151M2)
San Francisco, CA 94121
U.S.A.

W.R. BROWN
Gastroenterology Section
Veterans Administration Medical Center
1055 Clermont Street
Denver, CO 80220
and
University of Colorado
School of Medicine
Denver, CO 80220
U.S.A.

E.B. CHANG
Columbia University
College of Physicians and Surgeons
Department of Medicine, Gastrointestinal Unit
630 West 168th Street
New York, NY 10032
U.S.A.

J. CHRISTENSEN
Department of Internal Medicine
University of Iowa Hospitals and Clinics
Iowa City, IA 52242
U.S.A.

J.C. DAGORN
Unité de Recherches de Pathologie Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

A. DECARO
Unité de Recherches de Pathologie Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

J. DELVALLE
Gastroenterology Division
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, MI 48109
U.S.A.

M. FIELD
Columbia University
College of Physicians and Surgeons
Department of Medicine, Gastrointestinal Unit
630 West 168th Street
New York, NY 10032
U.S.A.

C.J. FIMMEL
Center for Ulcer Research and Education
VA Wadsworth Hospital, Building 114
Los Angeles, CA 90073
U.S.A.

A. GARNER
Imperial Chemical Industries
Bioscience Department
Mereside Alderley Park
Macclesfield, Cheshire SK10 4TG
U.K.

M.E. GLICK
Division of Gastroenterology N-3
Veterans Administration Medical Center
5901 East 7th Street
Long Beach, CA 90822
U.S.A.

H.I. GOLDBERG
Deparment of Radiology
University of California
San Francisco, CA 94143
U.S.A.

D.N. GRANGER
Department of Physiology
College of Medicine
University of South Alabama
Mobile, AL 36688
U.S.A.

S.L. HARPER
Department of Physiology
College of Medicine
University of South Alabama
Mobile, AL 36688
U.S.A.

W. HÖCHTER
I. Medizinische Abteilung
Städtisches Krankenhaus
Oskar-Maria-Graf-Ring 51
D-8000 München-Neuperlach 83
F.R.G.

D. HOLLANDER
University of California, Irvine
Medical Science Building
RM C340
Irvine, CA 92717
U.S.A.

E.J. ISRAEL
Combined Program in Pediatric Gastroenterology and Nutrition
Massachusetts General Hospital and Children's Hospital Medical Center
Harvard Medical School
Boston, MA 02115
U.S.A.

R.K. KERLAN Jr
Department of Radiology
University of California
San Francisco, CA 94143
U.S.A.

Y.S. KIM
University of California Service
Veterans Administration Medical Center
4150 Clement Street (151M2)
San Francisco, CA 94121
U.S.A.

H.R. KOELZ
Division of Gastroenterology
University Hospital, Inselspital
CH-3010 Bern
Switzerland

P.R. KVIETYS
Department of Physiology
College of Medicine
University of South Alabama
Mobile, AL 36688
U.S.A.

J. LAPOOK
Columbia University
College of Physicians and Surgeons
Department of Medicine, Gastrointestinal Unit
630 West 168th Street
New York, NY 10032
U.S.A.

R. LAUGIER
Unité de Recherches de Pathologie Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

C.W. LO
Combined Program in Pediatric
Gastroenterology and Nutrition
Massachusetts General Hospital and
Children's Hospital Medical Center
Harvard Medical School
Boston, MA 02115
U.S.A.

J.D. MENDLEIN
Center for Ulcer Research and Education
VA Wadsworth Hospital, Building 114
Los Angeles, CA 90073
and
Department of Physiology and Biophysics
University of California, Los Angeles
Los Angeles, CA 90024
U.S.A.

S.A. MÜLLER-LISSNER
Medizinische Klinik Innenstadt der
Universität München
Ziemssenstrasse 1
D-8000 München 2
F.R.G.

L. MULTIGNER
Unité de Recherches de Pathologie Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

R. OTTENJANN
I. Medizinische Abteilung
Städtisches Krankenhaus
Oskar-Maria-Graf-Ring 51
D-8000 München-Neuperlach 83
F.R.G.

M.A. PERRY
School of Physiology and Pharmacology
University of New South Wales
Kensington, NSW
Australia

W. RÖSCH
Krankenhaus Nordwest der Stiftung Hospital
zum Heiligen Geist
Steinbacher Hohl 2-26
D-6000 Frankfurt am Main 90
F.R.G.

R.I. ROTHSTEIN
Department of Medicine
Dartmouth-Hitchcock Medical Center
Hanover, NH 03755
U.S.A.

T.L. SACK
University of California Service
Veterans Administration Medical Center
4150 Clermont Street (151M2)
San Francisco, CA 94121
U.S.A.

J. SAHEL
Unité de Recherches de Pathologie
Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

H. SARLES
Unité de Recherches de Pathologie Digestive
U-31 INSERM
46 Boulevard de la Gaye
13258 Marseille Cédex 09
France

K. SCHULZE-DELRIEU
Division of Gastroenterology-Hepatology
Department of Medicine
University of Iowa Hospitals and Clinics
Iowa City, IA 52242
U.S.A.

J.W. SINGLETON
University of Colorado
Health Sciences Center
Gastroenterology Division B158
4200 East Ninth Avenue
Denver, CO 80262
U.S.A.

G.E. SLADEN
Guy's Hospital
Gastroenterology Unit
18th Floor, Guy's Tower
London, SE1 9RT
U.K.

W.A. WALKER
Combined Program in Pediatric
Gastroenterology and Nutrition
Massachusetts General Hospital
Harvard Medical School
Boston, MA 02115
U.S.A.

S.D. WALL
Department of Radiology
University of California
San Francisco, CA 94143
U.S.A.

J. WILEY
Gastroenterology Division
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, MI 48109
U.S.A.

D.L. WINGATE
Gastrointestinal Science Research Unit
London Hospital Medical College
26 Ashfield Street
London E1 2AJ
U.K.

B. WÖRMANN
I. Medizinische Abteilung
Städtisches Krankenhaus
Oskar-Maria-Graf-Ring 51
D-8000 München-Neuperlach 83
F.R.G.

T. YAMADA
Gastroenterology Division
Department of Internal Medicine
University of Michigan Medical Center
Ann Arbor, MI 48109
U.S.A.

Introduction

The third volume of *The Gastroenterology Annual* is considerably larger than the first two volumes, for a number of reasons. The period reviewed is longer, a year and a half (July 1982–December 1984), instead of the one year covered by each of the earlier volumes. More topics are included: to wit, neurophysiology and microbial infections of the gastrointestinal tract are covered for the first time: chapters on the colon, nutrition, gastrointestinal imaging and upper and lower gastrointestinal tract endoscopy were included in the first volume, but not in the second. Last, but certainly not least, investigation in our field is healthy and the number of published papers continues to increase. Thus, in spite of the authors' and editors' efforts to be considerate of our readers and to be concise, more pages were necessary.

Our objective is unchanged – to provide 'a scholarly, up-to-date, critical review of important new developments'. The emphasis, as before, is on areas where major advances have been made. These advances may be the achievements of new insights into normal function of the gastrointestinal tract, better understanding of pathophysiology or improvements in diagnosis and treatment of gastrointestinal disease. The past year and a half has been rich in such developments. Only a few will be mentioned to illustrate the scope of progress. A vast literature about peptic ulcer disease is published each year and grows progressively more monumental. The mucus–bicarbonate barrier and new classes of effective anti-ulcer drugs continue to excite interest. A number of approaches – immunological, genetic, microbiological – diminish the mystery of the cause of celiac disease. In the area of gastrointestinal cancer, oncogenes, the role of diet and environmental factors in cancer production, and the importance of precursor lesions to cancers of the esophagus and colon are some of the important topics. A new putative causative agent, a mycobacterium, is causing excitement among workers in inflammatory bowel disease. Investigators throughout the world have re-examined and reconfirmed the value of oral rehydration in the treatment of diarrhea in children. Monoclonal antibodies are being used to identify specific bacterial organisms which infect the gastrointestinal tract. The immunological functions of the intestinal tract are becoming increasingly complex. In the recent past, much has been learned about the transport of IgA through the liver and the role of intraepithelial lymphocytes, long regarded as a curiosity. Esophagologists are questioning the interpretation of manometric findings and have elucidated further the mechanisms of esophageal peristalsis and of mucosal injury by gastrointestinal content. The list goes on and on.

Once again, we are extremely grateful to our excellent group of authors for their dedication and commitment to this project.

FRED KERN Jr
ANDRÉ L. BLUM

Contents

1. The esophagus

K. SCHULZE-DELRIEU AND J. CHRISTENSEN

Progress has been made in understanding the mechanisms by which gastrointestinal secretions attack the integrity of the esophagus. Trypsin has emerged as a potential culprit in esophageal damage from 'alkaline' reflux. Acid causes loss of osmoregulation by esophageal epithelium and produces mucosal ischemia.

Theories of esophageal peristalsis have been revised so that there is now a role for both cholinergic and non-cholinergic nerves in the generation of a progressive ring contraction by esophageal muscle.

Studies on the diagnosis and management of esophageal disease have underscored many contentious issues. There is increasing doubt about the correlations between specific test abnormalities and symptoms and prognosis of esophageal disease. Is it justifiable to diagnose an esophageal abnormality in asymptomatic patients whose esophageal contractions fall outside the statistical range of an arbitrarily chosen group of controls? Do patients with abnormal reflux profiles, but without esophageal lesions or other reflux complications, need vigorous treatment, or is symptom control an adequate therapeutic goal?

MUCOSAL RESISTANCE

Saliva and esophageal acid clearance

Clearance of gastric acid from the esophagus is achieved principally by primary peristalsis and to a lesser degree by secondary peristalsis. Healthy subjects swallow in the waking state at a rate of about once per minute. Kapila and co-workers analyzed the interdependence of swallowing and flow of saliva (1). Atropine 12 μg/kg virtually abolished salivation and reduced the rate of swallowing by one-third. Cholinergic stimulation (bethanechol 5 mg s.c.) increased salivary output about 6-fold and almost tripled swallowing rate. Sucking a peppermint lozenge was about as effective as bethanechol; a dummy lozenge was less so. The authors view these results as circumstantial evidence that the rate of swallowing is determined by the rate of salivary secretion. According to ingrained medical beliefs, sucking and chewing are associated with the swallowing of air, which is often held responsible for epigastric distress. On the contrary, these data suggest that oral lozenges should be tested in the treatment of heartburn.

Trypsin in esophageal injury

Lillemoe and co-workers have assessed the effects of physiological concentra-

The Gastroenterology Annual 3
F. Kern Jr and A.L. Blum, editors

tions of trypsin, taurodeoxycholate and pepsin on the structure and function of the rabbit esophageal mucosa (2). Fluxes of H^+, glucose, potassium, water and hemoglobin were measured before and after perfusion of the test solution. The mucosal potential difference was recorded throughout the experiments. Pepsin and the alkaline test solution alone caused no changes in mucosal permeability. Trypsin and taurodeoxycholate both increased the efflux of water, potassium and glucose. Trypsin and taurodeoxycholate differed in their effects on hydrogen ion and hemoglobin flux: trypsin did not affect the hydrogen ion flux, but increased hemoglobin flux. The reverse occurred with taurodeoxycholate. After trypsin, but not taurodeoxycholate, there were striking epithelial erosions and submucosal hemorrhage (Fig. 1). Thus, the degree of functional barrier disruption and the degree of morphological injury do not necessarily correlate; the various components of gastroduodenal secretions cause esophageal injury through different mechanisms. Specific components like trypsin, rather than alkalinity *per se,* are likely to be responsible for esophageal damage from pancreaticobiliary secretions.

Additional evidence for the importance of trypsin in esophageal injury comes from the work of Salo and Kivilaakso at the University of Helsinki: these workers have previously shown that conjugated bile salts, as they are present in the normal gastrointestinal tract, are harmless to the esophageal mucosa unless combined with gastric acid (3). They also showed that the correlation between the severity of esophagitis after gastrectomy and the concentration of bile salts in the esophageal lumen is poor (4). They have now looked for a possible synergism of trypsin with taurocholate and cholate. Per-

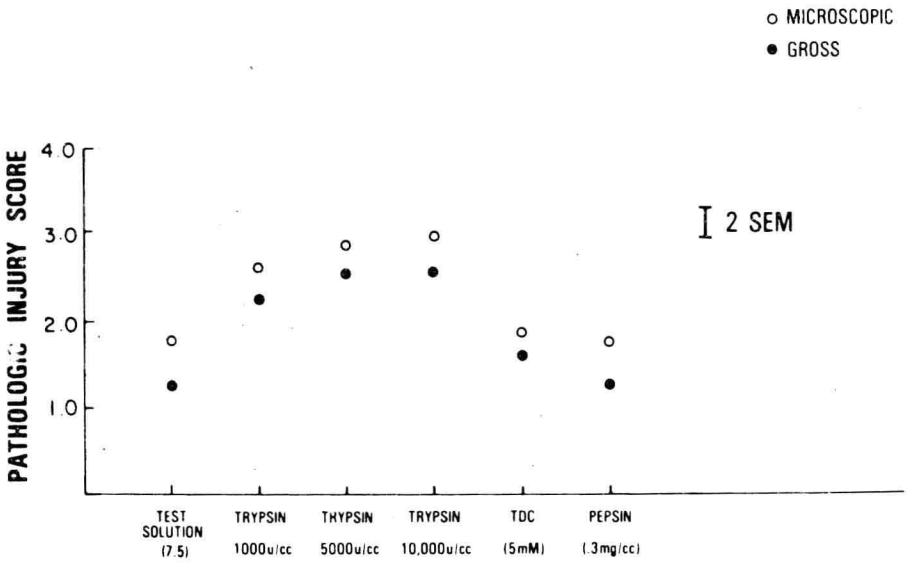

Fig. 1. Severity of gross and microscopic esophagitis in response to perfusion of alkaline test solution, various concentrations of trypsin, taurodeoxycholate (TDC) and pepsin. Esophagitis was scored between + (= normal) and ++++ (= extensive erosions with intramural hemorrhage). Reproduced from Lillemoe et al (2) by courtesy of the Editors of *Gastroenterology.*

fusion of cholate and taurocholate into the rabbit esophagus for $3\frac{1}{2}$ hours had little effect on the esophageal mucosa. Trypsin alone caused no gross esophageal lesions, but significantly increased the fluxes of sodium, water and erythritol, and decreased mucosal potential difference. Cholate, but not taurocholate, potentiated the effect of trypsin to the point where gross mucosal lesions occurred (5). The authors propose that trypsin, by digesting the intercellular substance, opens the way for deep mucosal penetration by bile acids.

Even though trypsin can harm the esophageal mucosa, there is no proof that so-called 'peptic' esophagitis is really tryptic esophagitis. Whether trypsin and other pancreatobiliary secretions get into the esophagus in the presence of an intact stomach is conjectural (6). Little and co-workers sought evidence for the importance of duodenogastric reflux in patients with normal stomachs by recording the gastric pH in 25 patients with proven gastroesophageal reflux. Ten patients had endoscopic evidence of esophagitis. Alkaline duodenogastric reflux, identified by the spontaneous occurrence of intense gastric alkalinity during fasting, was less frequent in reflux patients with esophagitis than in those without (7). Since patients with esophagitis also had delayed gastric emptying of labeled oatmeal, the unorthodox conclusion was reached that patients with reflux esophagitis have dysmotility of the stomach and of the pylorus.

Disruption of 'epithelial barrier' by acid

The normal esophageal mucosa is almost impermeable to hydrogen ion, glucose and other small molecules. The factors that contribute to the maintenance and the disruption of the esophageal mucosal barrier are only partly understood (8).

Esophageal epithelial damage from acute exposure to acid proceeds in two stages. During the first stage, water movement across the mucosa is increased in the presence of dilated intercellular spaces and a decreased epithelial resistance. During the second stage, cellular sodium transport is inhibited (9). The loss of cellular osmoregulation results in swollen and ruptured cells in the middle layers of the esophageal epithelium. The initial stage is accompanied by an increase in the potential difference (PD) that the mucosa generates, the last stage by a decrease. Orlando et al (10) have further clarified the mechanisms by which hydrogen ions cause changes in the esophageal mucosal PD and sodium transport. Acid perfusion of the rabbit esophagus caused an increase of the mucosal PD when hydrogen ion concentrations ranged between 20 and 40 mM, and a decrease when concentrations as high as 120 mM were used (Fig. 2). Intermediate concentrations (80 mM) caused an initial rise and a subsequent fall in mucosal PD. Esophageal mucosa which was removed while its PD peaked and mounted in a Ussing chamber did not show an increased PD, but did show increased net sodium transport through an amiloride-sensitive pathway. The unidirectional flux of all other ions was increased in proportion to the loss of tissue resistance. $(Na^+ + K^+)$ATPase activity was significantly inhibited following prolonged acid exposure. Thus, acidification of the esophageal mucosa increases its paracellular permeability and alters the permselectivity of the shunt pathway from a preference for cations to a preference for anions.

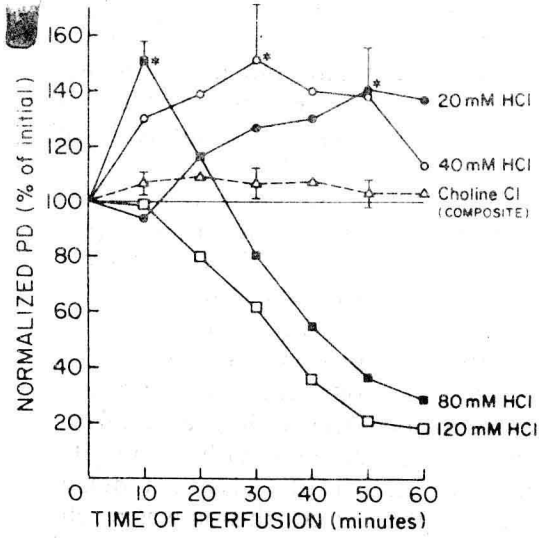

Fig. 2. Esophageal perfusion with 20 and 40 mM HCl is shown to increase esophageal potential difference (PD), while perfusion with 120 mM HCl decreases it. 80 mM HCl exhibits a biphasic response with an early increase in PD, followed by a sustained fall. *Significant difference when compared with choline Cl controls ($P < 0.05$). Reproduced from Orlando et al (10) by courtesy of the Editors of *American Journal of Physiology*.

The effect of acid injury on esophageal blood flow has been studied by Bass et al (11) who perfused the esophagus of anesthetized rabbits for two 1-hour periods with subulcerogenic concentrations of bile salts, pepsin or trypsin in the presence or absence of acid. When the mucosal barrier was broken by bile salts and trypsin at neutral pH, no acid back-diffusion occurred, but there was a dramatic increase in mucosal and, to a lesser extent, muscular blood flow as estimated by the microsphere method. However, when barrier disruption was accompanied by a significant back-diffusion of acid, no increase in total blood flow occurred. If blood flow had been initially increased by disrupting the epithelial barrier with neutral solutions, it was abolished by acid solutions. Acid, therefore, seems to promote mucosal acidosis and cell necrosis by inhibiting a compensatory tissue hyperemia. These data provide an explanation for the potentiating effect of acid on bile salt injury, in addition to the effects of acid on intercellular spaces, and of bile salt on cellular organelles (3, 12).

Prevention of esophageal injury by coating agents

While sucralfate has not been proven to be effective in the treatment of reflux esophagitis, the drug has aroused great scientific interest. Schweitzer et al (13) examined the effect of sucralfate on the production of esophagitis by acid, pepsin and taurocholate in a rabbit model. Sucralfate reduced the extent of lesions and the permeability changes produced by pepsin, but unfortunately had little benefit on the esophageal damage produced by taurocholate. Sucralfate formed a tenacious gel on the mucosal surface, but a clear solution of sucrose sulfate which did not form a gel was almost as protective

(see Fig. 3). No evidence was found that sucralfate inactivates pepsin directly. Preliminary in-vitro work has also shown the protective effect of sucralfate: Orlando exposed patches of esophageal mucosa in a Ussing chamber to 60 mM HCl. He measured short-circuit current and tissue resistance (14). When tissues were pretreated with sucralfate, the expected rise in short-circuit current and decline in tissue resistance failed to occur. Addition of sucralfate after resistance changes had been initiated by acid led to their reversal. These protective effects of sucralfate could not be explained by its acid-neutralizing capacity.

Wesdorp and colleagues performed a placebo-controlled trial of ranitidine in 36 patients with reflux esophagitis (15). By endoscopic and histological criteria, only 4 control patients improved after 6 weeks of trial period, whereas 15 out of 19 treated patients improved endoscopically and symptomatically. Ranitidine, like cimetidine, is beneficial in reflux esophagitis, but the treatment period may have to be extended beyond 6 weeks to achieve healing of all esophageal lesions and to prevent relapses.

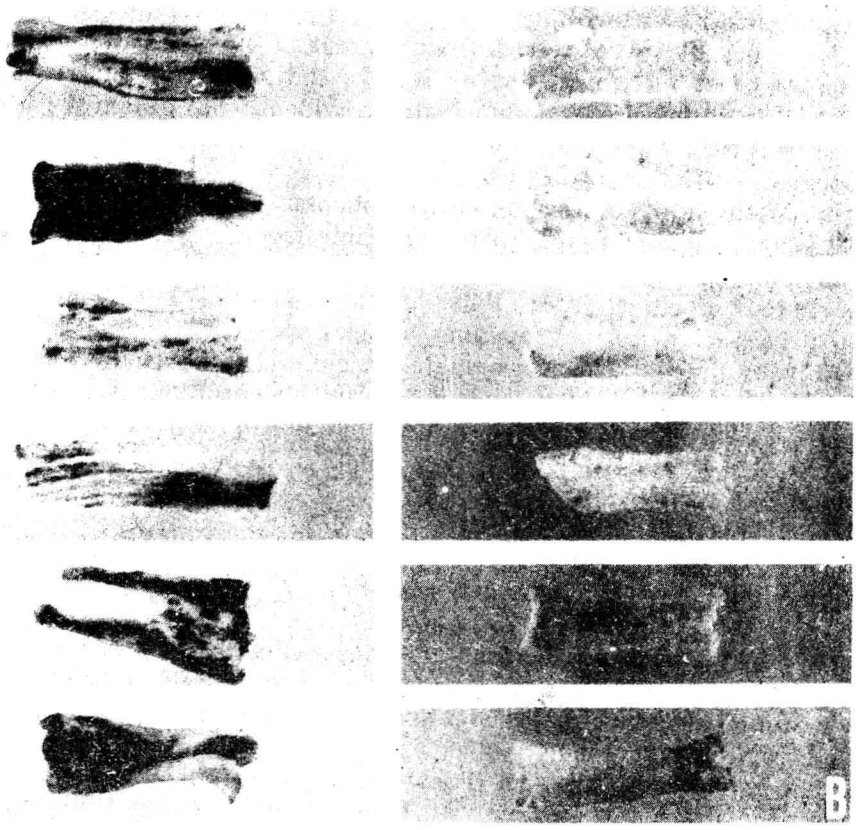

Fig. 3. Prevention of peptic esophagitis by sucralfate. (A) Esophagi exposed to pepsin alone. (B) Esophagi exposed to pepsin but treated with sucralfate. Reproduced from Schweitzer et al (13) by courtesy of the Editors of *Gastroenterology*.

The functions of the muscularis mucosae

To date, physiologists have not given much thought to what the function of the muscularis mucosae of the gut might be. Most work has focused on the small intestine, where it has been presumed that mucosal motions serve to promote absorption through their effect on mucosal blood or lymph flow. This reasoning cannot be applied to the esophagus where significant absorption does not occur, yet in which the muscularis mucosa is thicker than in any other gut segment.

The idea that the muscularis mucosae functions independently of the muscularis propria is quite likely in view of its recent pharmacological characterization by Christensen and Percy (16). These workers studied strips of esophageal muscularis mucosae from dog, cat and opossum in vitro to observe spontaneous activity and responses to a variety of drugs known to affect smooth muscle. Acetylcholine and histamine contracted all strips, acting on muscarinic and H_1-receptors respectively. Norepinephrine contracted tissues from dog and cat, an α-adrenoceptor-mediated affect, but not those of opossum. β-Adrenoceptor-activation relaxed the tissues. Cholecystokinin, vasoactive intestinal polypeptide and gastrin were without effect. Substance P was excitatory. These responses to peptides were tetrodotoxin-insensitive. Electrical field stimulation induced contractions which were neurogenic and cholinergic; no evidence was obtained for a non-adrenergic innervation. Evidence was obtained for α_1- and α_2-adrenoceptors in the opossum esophagus, α_2-adrenoceptors being inhibitory and located on cholinergic nerves.

In a careful study of the muscularis mucosae of the guinea-pig esophagus, Kamikawa et al (17) found that muscarinic receptors are mainly linked to calcium ion channels which are independent of changes in muscle cell membrane potentials. In contrast, those of the longitudinal ileal muscle of the same species act mainly by opening voltage-dependent calcium channels but negligibly by opening receptor-operated calcium channels or by the release of intracellularly stored calcium. Thus, muscarinic receptor heterogeneity includes differences not only in receptor activation but also in receptor action.

THE ESOPHAGEAL SPHINCTERS

The upper esophageal sphincter and aspiration

A variety of pulmonary conditions are associated with gastroesophageal reflux. In infants, apnea and the sudden infant death syndrome are suspected to be complications of gastroesophageal reflux. In both children and adults, recurrent bronchitis, recurrent pneumonia and intermittent asthma have been linked to reflux. A confounding problem is that respiratory problems from reflux often occur in the absence of gastrointestinal symptoms, and that reflux may be the consequence rather than the cause of respiratory distress. Reviews of the subject have appeared (18–20).

Interest in the pathophysiology of reflux-related respiratory problems has been rekindled by the discovery that esophageal receptors mediate reflex re-

sponses (21). As reviewed by Winship (22), the upper esophageal sphincter (UES) responds to esophageal distention and acidification with forceful contraction. While this reflex contraction of the UES is undisputed, there is considerable controversy about the 'hypertensive UES' or its failure to relax (so-

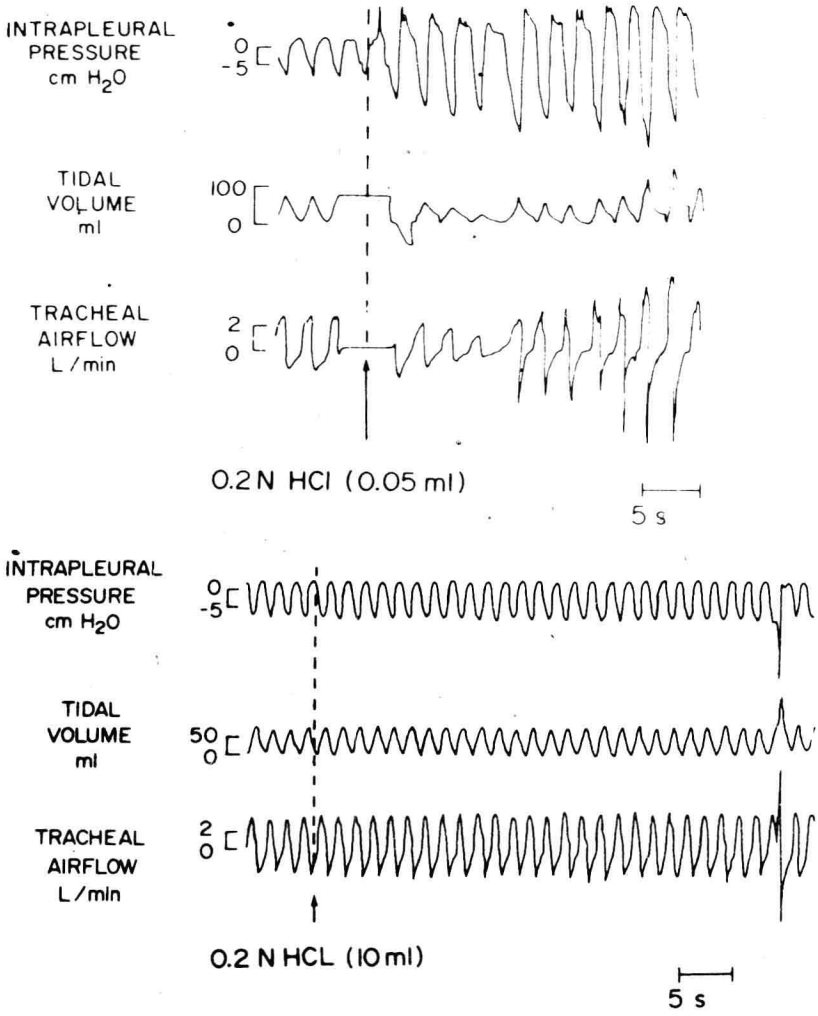

Fig. 4. Top: Lung mechanics after intratracheal acid infusion. Baseline measurements are to the left of the dotted line. The interruption of the flow and volume curves reflect the pneumotachograph being disconnected from the tracheostomy tube to allow the bolus infusion of 0.05 ml of 0.2 N HCl into the trachea. Immediately after tracheal acidification, there is a large increase in intrapleural pressure associated with a decrease in tidal volume and tracheal air flow. Within 10 s of stimulus, there is a gradual increase in flow and volume, yet both inspiratory and expiratory pressures remain increased. *Bottom:* Lung mechanics after intraesophageal acid infusion. Baseline measurements are to the left of the dotted, vertical line. Commencing at the time indicated by the arrow, 10 ml of 0.2 N HCl was infused over 20 s at a point midway between the proximal border of the lower and upper esophageal sphincter. Close inspection reveals a slight increase in both inspiratory and expiratory intrapleural pressure, as well as tracheal air flow. Reproduced from Tuchman et al (24) by courtesy of the Editors of *Gastroenterology*.